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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/001003	01.04.2004	01.04.2003

International Patent Classification (IPC) or both national classification and IPC
C12P7/62, C12P17/06, C07C67/00, A61K31/215

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Devijver, K Telephone No. +31 70 340-4124

Form PCT/ISA/237 (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/001003

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25

because:

☒ the said international application, or the said claims Nos. 25 (as to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10-19
	No:	Claims	1-9,20-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

Claim 25 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

The separate inventions/groups of inventions are:

1. claims: 1-22:
Process for producing substantially pure pravastatin, the process comprising culturing microorganisms under conditions capable of converting compactin to pravastatin by maintaining a concentration of compactin not less than 300 µg/ml during the process.

2. claims: 23-25:
Substantially pure pravastatin, a pharmaceutical composition comprising said pravastatin and a method of treating hypercholesterolemia comprising administering said pharmaceutical composition.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons.

A process for producing pravastatin, the process comprising culturing microorganisms under conditions capable of converting compactin to pravastatin by maintaining a concentration of compactin not less than 300 µg/ml during the process, and substantially pure pravastatin, a pharmaceutical composition comprising said pravastatin and a method of treating hypercholesterolemia comprising administering said pharmaceutical composition were all already state of the art before the priority date of the present application.

In particular, document D1 (WO9845410) discloses (cf. claims 2, 4 and page 9 lines 15-27) a method for producing pravastatin from hydroxylation of compactin by using a production medium wherein the compactin concentration is maintained in a range of 0.1-5.0%. Moreover, documents D2 (US2002/0081675) (cf. page 6 paragraph 44 and

page 1) and D3 (WO0017182) (cf. abstract, claims 26-29 and examples 1-5) disclose substantially pure pravastatin up to purities of 99.5% and even 99.8%, as well as a pharmaceutical composition comprising said pravastatin and a method of treating hypercholesterolemia comprising administering said pharmaceutical composition.

In the light of the above mentioned prior art, the problems and corresponding solutions of the present application can be summarized as follows:

problem 1: providing a further process for producing pravastatin;

solution 1: process for producing pravastatin, the process comprising culturing microorganisms under conditions capable of converting compactin to pravastatin by maintaining a concentration of compactin not less than 300 µg/ml during the process;

problem 2: providing a further substantially pure pravastatin composition;

solution 2: substantially pure pravastatin, a pharmaceutical composition comprising said pravastatin and a method of treating hypercholesterolemia comprising administering said pharmaceutical composition.

The ISA considers that, due to the fact that a process for producing pravastatin, the process comprising culturing microorganisms under conditions capable of converting compactin to pravastatin by maintaining a concentration of compactin not less than 300 µg/ml during the process, and substantially pure pravastatin, a pharmaceutical composition comprising said pravastatin and a method of treating hypercholesterolemia comprising administering said pharmaceutical composition were known (cf. D1-D3), due to the essential differences between the above mentioned problems and their corresponding solutions, and due to the fact that no other technical feature can be distinguished which in the light of the prior art could be regarded as special technical feature, there is no single inventive concept underlying the plurality of claimed inventions, and an objection for non-unity of invention has to be raised under PCT Rule 13.1.

Re Item V.

1 The following documents are referred to in this communication:

D1: WO 98/45410 A (YUNGJIN PHARMACEUTICAL IND CO ; KIM JI YOON (KR); LEE JOO KYUNG (KR);) 15 October 1998 (1998-10-15)
D2: US 2002/081675 A1 (HORVATH GYULA ET AL) 27 June 2002 (2002-06-27)
D3: WO 00/17182 A (LEK TOVARNA FARMACEVTSKIH ; MILIVOJEVIC DUSAN (SI); BASTARDA ANDREJ (S) 30 March 2000 (2000-03-30)
D4: GRAHEK R ET AL: "Chromatographic purification of some 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors" JOURNAL OF CHROMATOGRAPHY, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 918, no. 2, 25 May 2001 (2001-05-25), pages 319-324, XP004239132 ISSN: 0021-9673

2 NOVELTY (Art. 33(2) PCT) - INVENTIVE STEP (Art. 33(3) PCT)

2.1 Document D1 discloses (cf. claims 2, 4 and page 9 lines 15-27) a fermentative process for producing pravastatin, the process comprising culturing microorganisms belonging to the Streptomyces genus under conditions capable of converting compactin to pravastatin by maintaining a concentration of compactin not less than 300 µg/ml (= 0.03%) during the process, namely in a range of 0.1-5%. Consequently, D1 anticipates the subject-matter of independent claim 1. Hence the subject-matter of this claim is not new (Art. 33(2) PCT).

2.2 Dependent claims 2-22 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Art. 33(2) and (3) PCT).

2.3 In particular, claim 5 lacks novelty in view of D1, because it refers to the range of "about 300-900 µg/ml" (= 0.03-0.09%). The word "about" is vague and indefinite and as such renders the scope of said claim unclear (Art. 6 PCT). Moreover, "about 0.09%" could in fact be 0.1% (cf. D1) and therefore, said claim lacks novelty (Art. 33(2) PCT).

2.4 Documents D2 (cf. page 6 paragraph 44 and page 1), D3 (cf. abstract, claims 26-29 and examples 1-5) and D4 (cf. page 322) disclose substantially pure pravastatin up to purities of 99.5%, 99.8% and even 99.83% respectively, as well as a pharmaceutical composition comprising said pravastatin and a method of

treating hypercholesterolemia comprising administering said pharmaceutical composition. Consequently, the documents D2, D3 or D4 anticipate the subject-matter of claims 23-25 (Art. 33(2) PCT) (cf. also present description page 5 lines 20-24 and page 8 lines 22-24).

2.5 Thus, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9 and 20-25 is not new in the sense of Article 33(2) PCT.

2.6 Thus, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-25 does not involve an inventive step in the sense of Article 33(3) PCT.

2.7 For the assessment of present claim 25 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.